REMARKS

Status of the application

Claims 1-10, 14-17, 19-22 and 27-33 are pending in the application. Among the pending claims, claims 10, 14-15, 17 and 19 are withdrawn from consideration by the Examiner as directed to non-elected inventions. Claims 1-9, 16, 20-22 and 27-33 are under examination and remain rejected in the instant Office Action.

With entry of the present response, claims 20-22 have been canceled without prejudice. The claim cancellation was made as a further effort to facilitate prosecution of the subject application, and should not be be construed as acquiescence of any ground of rejections. Applicants submit the following remarks to address the substantive issues raised in the instant Office Action.

Rejection under 35 U.S.C. §103

Applicants present the following remarks to address the alleged obviousness of the pending claims, which is the only substantial issue remaining in the subject application. Specifically, claims 1-8, 16, 20, 21 and 29 remain rejected as allegedly being obvious over Adam et al. (US Patent No. 6407094) in view of Corsi et al. (US 2003/0195139) or Chiamulera et al. (Nat. Neurosci. 4:873-4, 2001). Claims 9, 22, 27, 28, 32 and 33 are rejected as allegedly obvious over Chiamulera et al. in view of Adam et al. Further, claims 29, 30, 31 and 33 are rejected as allegedly obvious over Bear et al. (US Patent No. 6916821) in view of Adam et al. Applicants respectfully traverse the rejection for the reasons on record and the additional remarks presented below.

1. Expert declaration re non-obviousness of combining mGluR2/3 antagonist and mGluR5 antagonist

Applicants submit herewith a declaration of co-inventor Dr. Athina Markou. Dr. Markou is an expert in the field of neuropharmacology and substance addiction, and

has published extensively on addictive disorders and drug dependence. In her declaration, Dr. Markou points out that, due to their different locations, mGluR5 receptors and mGluR2/3 receptors have different functions in glutamate signaling (e.g., postsynaptically located mGluR5 receptors are excitatory, and presynaptically located mGluR2/3 receptors are inhibitory). Dr. Markou then notes that antagonizing both mGluR5 and mGluR2/3 would therefore be expected to have opposite effects on glutamate signaling. Dr. Markou further cites several peer-reviewed publications as further evidence of the non-obviousness nature of combining a mGluR2/3 antagonist and a mGluR5 antagonist in treating addictive disorders. These publications reported experimental results suggesting that, but for the teachings of the subject invention, one would indeed expect opposite behavioral and neurochemical effects of mGluR2/3 antagonists and mGluR5 antagonists.

In her declaration, Dr. Markou further comments on one of the key references cited by the Examiner, Fundytus et al., British J. Pharmacol. 120:1015-20, 1997. Dr. Markou states that the Fundytus et al. reported prevention of the development of morphine dependence in rats with mGluR antagonists (e.g., MCPG), not treatment of withdrawal symptoms in rats already having morphine dependence.

The evidentiary value of Dr. Markou's declaration with respect to the non-obvious nature of the subject invention is further discussed in more detail herein. It is submitted that Dr. Markou's stature as an expert in the field merits appropriate deference. "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Guidelines for Examination of Applications for Compliance with the Utility Requirement at §B4. Appropriate deference by an Examiner to the opinion of an expert is also emphasized by *In re Soni* which holds that the opinion of an expert must be accepted "in the absence of evidence to the contrary." 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

2. Fundytus et al. does NOT teach "treating morphine withdrawal symptoms" with dual antagonist MCPG

In reply to Applicants' previous response, the Examiner states in the instant Office Action that Fundytus et al. teaches a method of "treating morphine withdrawal symptoms" with dual antagonist MCPG which "do not neutralize or hinder each other in regards to providing therapeutic effects." Applicants respectfully note that the Examiner's assertion is simply incorrect.

As explained in Applicants' previous response, substance use/abuse and substance dependence are different concepts that require different means for treatment and intervention. Consistently, as clarified below, Fundytus et al. reports that mGluR antagonists (e.g., MCPG) can prevent development of morphine dependence in rats that start "using" morphine but are not effective in treating withdrawal symptoms in rats once dependence is already developed. The presently claimed invention relates to methods and compositions for treating metabotropic glutamate disorders such as addictive disorders and depression. The invention is directed to reducing, alleviating or eliminating withdrawal symptoms (e.g., depression) associated with cessation of substance use in subjects that have an existing addictive disorder. The invention is not directed to preventing the development of substance dependence in subjects that are not already suffering from substance dependence.

As noted by Dr. Markou in the attached declaration, Fundytus et al. reported that administration of MCPG prevented the development of morphine dependence in rats simultaneously administered with morphine. In other words, this reference might have taught that antagonizing both mGluR2/3 and mGluR5 via MCPG would not diminish a therapeutic effect in preventing the development of substance dependence. However, Fundytus et al. did not show that mGluR antagonists are effective to treat rats that have already developed morphine dependence. Fundytus et al. did not provide any teaching or suggestion that would otherwise alleviate one's concerns about the potential opposite effects of antagonizing mGluR2/3 and antagonizing mGluR5 in the treatment of

withdrawal symptoms in subjects with substance dependence or addictive disorders. Instead, Fundytus et al. expressly stated that treatment with mGluR antagonists (including MCPG) is not effective in ameliorating dependence symptoms once dependence had developed.

If a dual antagonist of mGluR2/3 and mGluR5 like MCPG is shown to be ineffective in treating substance dependence in Fundytus et al., how can one logically conclude that the combination of a mGluR2/3 (mono) antagonist and a mGluR5 (mono) antagonist would have no neutralizing or opposing effects? To the contrary, Applicants submit that one is likely to draw the exact opposite conclusion from Fundytus et al. That is, one would reasonably infer that the lack of efficacy of MCPG in treating dependence symptoms could be due to the opposite effects of antagonizing both mGluR2/3 and mGluR5. One would further conclude that the combination of a mGluR2/3 mono antagonist and a mGluR5 mono antagonist would similarly be ineffective, just like the result obtained with dual antagonist MCPG as reported in Fundytus et al.

3. Relevance of additional reference cited by the Examiner

As further support of the alleged teaching of Fundytus et al., the Examiner cited Bradley et al. (Addiction 82:1139-42, 1987). The Examiner stated that Bradley et al. teaches that "withdrawal symptoms are also experienced by opiate addicts," that "withdrawal symptoms are feared by many addicts ... and provide negative reinforcement for continued drug taking," and that "conditioning models emphasize the role of conditioned withdrawal in precipitating relapse." Applicants do not dispute that, as it is well known in the art, withdrawal symptoms are experienced or feared by drug addicts (i.e., subject already suffering from dependence). However, with due respect, Applicants fail to see any relevance of Bradley et al. and the quoted statements thereof to the issue of whether Fundytus et al. taught treatment of withdrawal symptoms in subjects that have already developed drug dependence. As clarified above, Fundytus et al. only taught therapeutic benefits of the disclosed mGluR antagonists in preventing

the development of morphine dependence. It does not show that the antagonists are effective in treating withdrawal symptoms associated with existing drug dependence. On the other hand, the teachings of Bradley et al. relate to "addicts" who are already experiencing drug dependence. Bradley et al. does not address subjects who start using drug and will likely develop drug dependence. It certainly does not teach or suggest that an efficacy in preventing the development of substance dependence will also indicate an efficacy in treating withdrawal symptoms once substance dependence is developed in a subject. Thus, Bradley et al. does not even remotely remedy the deficiency of Fundytus et al. that is needed in order to render the subject invention obvious.

4. Non-obviousness nature of the present invention

The instant rejections are primarily based on the Examiner's belief that one would be motivated to combine a mGluR2/3 antagonist and a mGluR5 antagonist because both have been taught in the art to "treat substance abuse, depression, and/or anxiety . . . " Applicants acknowledge that both mGluR2/3 receptors and mGluR5 receptor may have been implicated in certain addictive disorders. However, it would be counter-intuitive (hence, non-obvious) to combine a mGluR2/3 antagonist and a mGluR5 antagonist in the treatment of addictive disorders (i.e., disorders associated with drug dependence). As stated in Dr. Markou's declaration, this is because presynaptically located mGluR2/3 receptors and postsynaptically located mGluR5 receptor have opposing effects on glutamate signaling. Specifically, blockade of the excitatory Group I glutamate receptors (e.g., mGluR5) will result in decreased glutamate signaling), and blockade of the inhibitory Group I mGluR2/3 receptors will result in increased release of glutamate and thus increases glutamate signaling. As discussed below, the counter-intuitive nature of combining a mGluR5 antagonist and a mGluR2/3 antagonist and the opposite effects that can result therefrom is further demonstrated in the references cited in Dr. Markou's declaration.

First, Dr. Markou's cited several studies which suggest that mGluR2/3 antagonist and mGluR5 antagonists can have opposing effects on neurochemical effects on glutamate neurotransmission. For example, Mills et al. (J. Neurochem. 79: 835-48, 2001) employed adult male Sprague-Dawley rats that were impact injured at T10 with an NYU impactor (12.5 mm drop) to examine the role of mGluRs in the increase in extracellular excitatory amino acids following spinal cord injury. Drugs, including the mGluR5 antagonist MPEP and the mGluR2/3 agonist LY341495, were injected into the epicenter of injury. Excitatory amino acids, including glutamate and GABA, where collected by microdialysis fibers inserted 0.5 mm caudal from the edge of the impact region and quantified by HPLC. Mills et al. found that the mGluR5 antagonist MPEP decreased excitatory amino acid concentrations, while treatment with the mGluR2/3 agonist LY 341495 increased excitatory amino acid levels. Similarly, Xi et al. (J. Pharmacol. Exp. Ther. 300:162-71, 2002) reported that the mGluR2/3 antagonist LY143495 increased extracellular glutamate in the nucleus accumbent. By contrast, the mGluR5 antagonist MPEP inhibited glutamate release in vitro and in vivo in the corpus striatum (Thomas et al., Neuropharmacology 41: 523-7 2001) and the periaqueductal grey (de Novellis et al., Eur J Pharmacol 462: 73-81 2003).

In addition, as noted in Dr. Markou's declaration, the opposing activities of mGluR2/3 antagonist and mGluR5 antagonists on behavioral effects are also reported in the art. For example, Sharko et al. (Alcohol. Clin. Exp. Res. 32: 67-76, 2008) determined if mGluRs modulate the acute sedative-hypnotic properties of ethanol in C57BL/6J mice. Sedation was measured by locomotor activity. Hypnosis was measured by duration of loss of the righting reflex. The authors reported that the mGluR5 antagonist MPEP (10 and 30 mg/kg) significantly enhanced both the sedative and hypnotic effects of ethanol, while the mGluR2/3 antagonist LY341495 (10 and 30 mg/kg) significantly decreased the sedative hypnotic effects of ethanol.

From these references cited by Dr. Markou as well as Fundytus et al., it is an escapable conclusion that one of ordinary skill in the art would not have thought about

combining a mGluR5 antagonist and a mGluR2/3 antagonist in treating an addictive disorder. Rather, all the available evidence suggests that one would likely be led away from such an approach. Thus, no prima facie case of obviousness could be established against the subject invention. Further, assuming for the sake of argument that a prima facie case of obviousness was indeed present with regard to the pending claims, the secondary evidence on record and additional clarifications provided by Applicants herein (e.g., teaching away by Fundytus et al.) are nonetheless sufficient to rebut the Examiner's conclusion. *See* MPEP § 2142.

To summarize, the present invention is nonobvious because the skilled artisan would not have reasonably expected to combine a mGluR2/3 antagonist and a mGluR5 antagonist to treat substance dependence mediated by glutamate receptors. Instead, one would very well be led away from the present invention by the teachings of the art, e.g., the opposing activities of the two classes of glutamate receptors, as well as Fundytus et al. which disclosed that a dual antagonist of mGluR2/3 antagonist and mGluR5 is not effective in treating morphine dependence. Accordingly, Applicant respectfully requests that the present rejection be withdrawn for the reasons of record and for the additional reasons stated above.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the claims now pending in the subject patent application are in condition for allowance, and notification to that effect is earnestly requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937.

The Director is hereby authorized to charge our Deposit Account No. 19-0962 in the event that there are any further charges associated with the present Response or any Response in connection with this application.

Respectfully submitted,

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Date

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